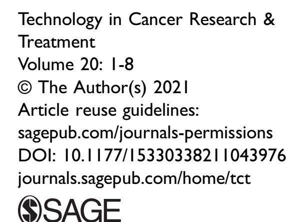
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MiR-18a-5p Facilitates Progression of Hepatocellular Carcinoma by Targeting CPEB3

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Abstract

Objective: To explore the function of the miR-18a-5p/CPEB3 axis in regulating the occurrence of hepatocellular carcinoma (HCC). **Methods:** Differentially expressed miRNAs and mRNAs were acquired by bioinformatics analysis. qRT-PCR was used for miR-18a-5p and CPEB3 mRNA expression detection. Cell functional assays were implemented to examine the biological functions of HCC cells. The binding relationship between miR-18a-5p and CPEB3 was verified by a dual luciferase assay. **Results:** In HCC, miR-18a-5p was remarkably highly expressed, while CPEB3 was markedly lowly expressed. HCC cell progression was facilitated after cells transfecting miR-18a-5p mimic, whereas silencing miR-18a-5p caused the opposite result. Overexpressing CPEB3 could restore promoting effect of miR-18a-5p on the growth of HCC cells. **Conclusion:** Oncogene miR-18a-5p accelerates malignant phenotype by suppressing CPEB3. MiR-18a-5p/CPEB3 axis in HCC identified in this study provides a new target for HCC treatment.

Keywords

miR-18a-5p, CPEB3, hepatocellular carcinoma, invasion, migration proliferation

Background

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors in the world.[1,2] According to statistics, Chinese sufferers account for about 55% of global HCC patients.[3] Most of the patients were already in the advanced stage of liver cancer when they were diagnosed, often with metastasis, or easy to develop resistance to chemotherapy, resulting in poor prognosis.[4,5] New potential therapeutic targets are in urgent need for HCC.

Gene therapy has become a research hotspot in recent years. MiR-18a was dysregulated in human cancers and related to tumor development. Studies exhibited that functions of miR-18a vary in diverse tumors, and miR-18a can be a tumor inhibitor or an oncogene. MiR-18a-5p is a main mature body of miR-18a, and its role in tumors has been widely studied.[6–8] For example, miR-18a-5p downregulates CDC42 in colorectal cancer cells, thereby inhibiting tumorigenesis.[6] Other studies showed increased miR-18a-5p expression in various cancers, which promotes tumorigenesis by regulating cell growth.[7–10] For instance, miR-18a-5p promotes the occurrence of HCC by targeting IRF2.[11] Lu et al[12] proposed that miR-18a-5p promotes metastasis of osteosarcoma by targeting IRF2. Zhou et al[13] found that miR-18a-5p facilitates renal cell carcinoma cell proliferation, migration, and invasion, and inhibits cell apoptosis. Zhang et al[14] demonstrated that miR-18a-5p facilitates HCC cell proliferation by targeting IRF2 and CBX7. Although miR-18a-5p has been studied in HCC, its underlying mechanisms remain to be further explored.

CPEB3 modulates the translation process by regulating cytoplasmic polyadenylation.[15] Ke et al[16] proposed that low CPEB3 expression is linked with an adverse prognosis of HCC patients, and knockdown of CPEB3 could reduce the inhibitory effect of miR-224 down-regulation on Huh-7 cells. In conclusion, we believed that both CPEB3 and miR-18a-5p may be related to the malignant progression of HCC. In addition, we analyzed downstream target genes of miR-18a-5p through bioinformatics analysis and found that 4 genes (CPEB3, CYP39A1, ESR1, and GPM6a) could bind with miR-18a-5p, among which CPEB3 had a significant correlation with miR-18a-5p. Hence, CPEB3 was selected as the research object here. Some studies indicated

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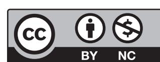
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that CPEB3 is abnormally expressed in some tumors, and can influence the progression of cancer. Hansen et al[17] found that CPEB3 is down-regulated in cervical cancer. The study of Zhang et al[18] manifested that CPEB3 inhibits EMT of HCC cells, and mice with CPEB3 knockout are more prone to develop HCC and lung metastasis. These studies suggest that CPEB3 is vital in modulating the growth and development of various tumors, including HCC. However, the mechanism of CPEB3 regulating HCC remains unclear.

Hence, we aim to clarify the possible mechanism of miR-18a-5p affecting the development of HCC, and we expect to bring new hope for HCC therapy.

Material and Methods

Bioinformatics Approaches

MiRNA and mRNA expression data of HCC were acquired from The Cancer Genome Atlas (TCGA) database. EdgeR package helped to screen differentially expressed genes (DEGs) ($|logFC|>2$, $padj<0.01$). Survival analysis of the target miRNA was conducted. Then, mirDIP and starBase were consulted to predict potential targets of the miRNA. Afterward, a Venn diagram was plotted with differentially down-regulated mRNAs to find the potential target gene.

Cell Incubation

Human HCC cell lines SMMC7721 (BNCC338089), HepG2 (BNCC338070), and human normal liver cell line HL-7702 (BNCC351907) were from BeNa Culture Collection (Shanghai, China). HL-7702 and SMMC7721 were incubated in Roswell Park Memorial Institute-1640 with 10% fetal bovine serum (FBS). HepG2 was cultivated in Dulbecco's Modified Eagle's Medium-high glucose (DMEM-H) containing 10% FBS. These cells were grown at standard conditions.

Transfection Treatment of Cells

MiR-18a-5p inhibitor (inhibitor), miR-18a-5p mimic (mimic), and their respective negative controls (NCs) were from RiboBio. CPEB3 overexpression plasmid (oe-CPEB3) and NC (oe-NC) were bought from GeneChem (Shanghai, China). The above gene fragment or plasmid was transfected into SMMC7721 and HepG2 cell lines with Lipofectamine 2000 (Thermo Fisher Scientific).

qRT-PCR

Total RNA was isolated using TRIzol reagent (Life Technologies). Using SYBR miRNA RT-PCR kit or Prime Script RT Master Mix (Takara) to reversely transcribe miRNA or mRNA into cDNA. MiR-18a-5p and CPEB3 mRNA expression was measured by Applied Biosystems 7500 real-time PCR instrument (Thermo Fisher Scientific, Inc.). GAPDH and U6 served respectively as internal controls for CPEB3 and miR-18a-5p. Primer sequences were shown in Table 1.

Western Blot

Cell lysates were extracted with RIPA lysate buffer (Beyotime). The concentration of proteins was determined by a BCA protein assay kit (Beyotime). Proteins were separated and transferred onto a PVDF membrane (Millipore). The membrane was blocked with 5% skim milk for 2 h and reacted with primary antibodies overnight at 4 °C. The primary antibodies were all rabbit polyclonal antibodies, including anti-CPEB3 (NBP1-56919, 1.0 µg/mL, Novus Biologicals) and anti-GAPDH (ab9485, 1:2500, Abcam). Later, the membrane was cultured with secondary antibody IgG (ab6721; 1:5000; Abcam). An enhanced chemiluminescence (ECL) kit was used to detect protein signals (GE Healthcare).

MTT Assay

Transfected cells (5×10^3 cells/well) were inoculated into 96-well plates. After 1, 2, 3, 4, or 5 d, the cells were added to each well and incubated with 20 µL MTT solution at 37 °C for 4 h, and then added with 100 µL buffer solution at 37 °C for overnight. Absorbance at 570 nm was read by a spectrophotometer (Molecular Devices).

Wound Healing Assay

Cells were inoculated in 6-well plates. When the cell fusion rate reached 80%, a sterile pipette tip (200 µl) was used to scrape the cell monolayer. The wells were flushed twice in the medium to remove isolated cells. A serum-free medium was added and cell migration was observed 24 h later.

Transwell Assay

Cells were seeded in the Transwell upper chamber of a 24-well plate (8-µm pore size, BD Biosciences). After incubation, invading cells in the lower chamber were treated with 0.2% crystal violet. The number of stained cells was then counted.

Dual-Luciferase Assay

The 3′UTR of wild-type (Wt) or mutant (Mut) CPEB3 mRNA was cloned into pmirGLO (Promega) vectors to construct CPEB3-Wt and CPEB3-Mut vectors. Then, the plasmid vectors and miR-18a-5p mimic or NC-mimic were co-transfected into HepG2/SMMC7721 cell line. After 24 h, luciferase activities of cells were determined using a dual-luciferase assay system (Promega).

Statistical Analysis

GraphPad Prism 6.0 (Lajolla) was used to treat data. Each experiment was repeated 3 times. Results were expressed as

Table 1. Primer Sequences.

Gene	Forward primer sequence (5′−3′)	Reverse primer sequence (5′−3′)
GAPDH	CGGAGTCAACGGATTTGGTCGTAT	AGCCTTCTCCATGGTGGTGAAGAC
CPEB3	GAGCTGTTGAACTGGCAATG	ACTGCAGACAGGTGACGTTG
miR-18a-5p	GATAGCAGCACAGAAATATTGG C	GTGCAGGGTCCGAGGT
U6	CGCGCTTCGGCAGCACATAT ACT	ACGCTTCACGAATTTGCG TGTC

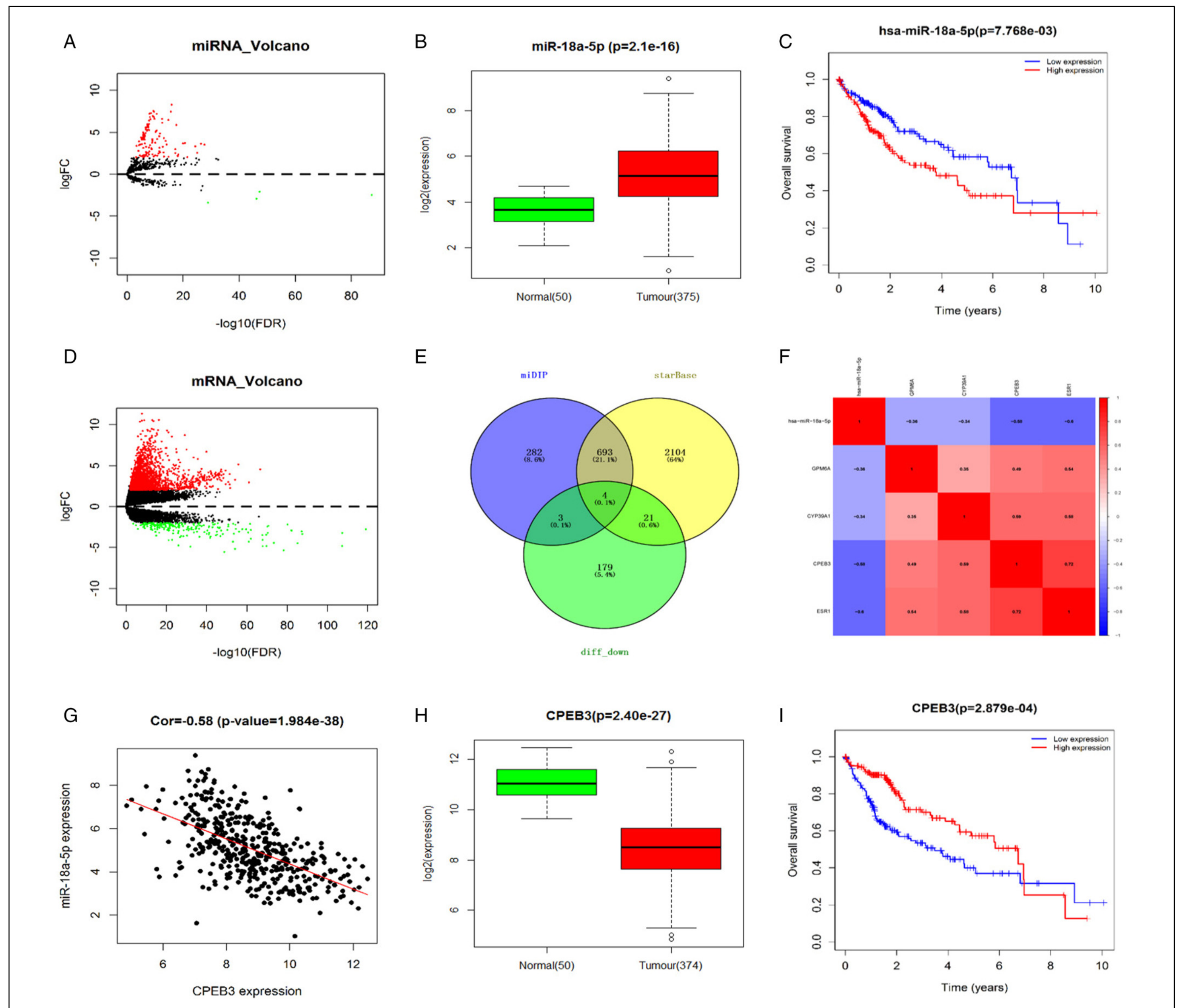

Figure 1. MiR-18a-5p correlates with CPEB3 in HCC. (A) Differential miRNAs in HCC (green: downregulated miRNAs, red: upregulated miRNAs); (B) MiR-18a-5p expression in TCGA with the green for normal group and the red for tumor group; (C) Survival significance of miR-18a-5p (red curve: high expression, blue: low expression); (D) Volcano map of differential mRNAs in HCC (green: downregulated mRNAs, red: upregulated miRNAs); (E) Venn diagram of the differentially downregulated mRNAs and predicted target genes of miR-18a-5p; (F) Correlation between miR-18a-5p and its predicted target genes; (G) Correlation of miR-18a-5p and CPEB3; (H) Relative expression of CPEB3, with the green for normal group and the red for tumor group; (I) Survival significance of CPEB3 (red cure: high expression, blue curve: low expression).

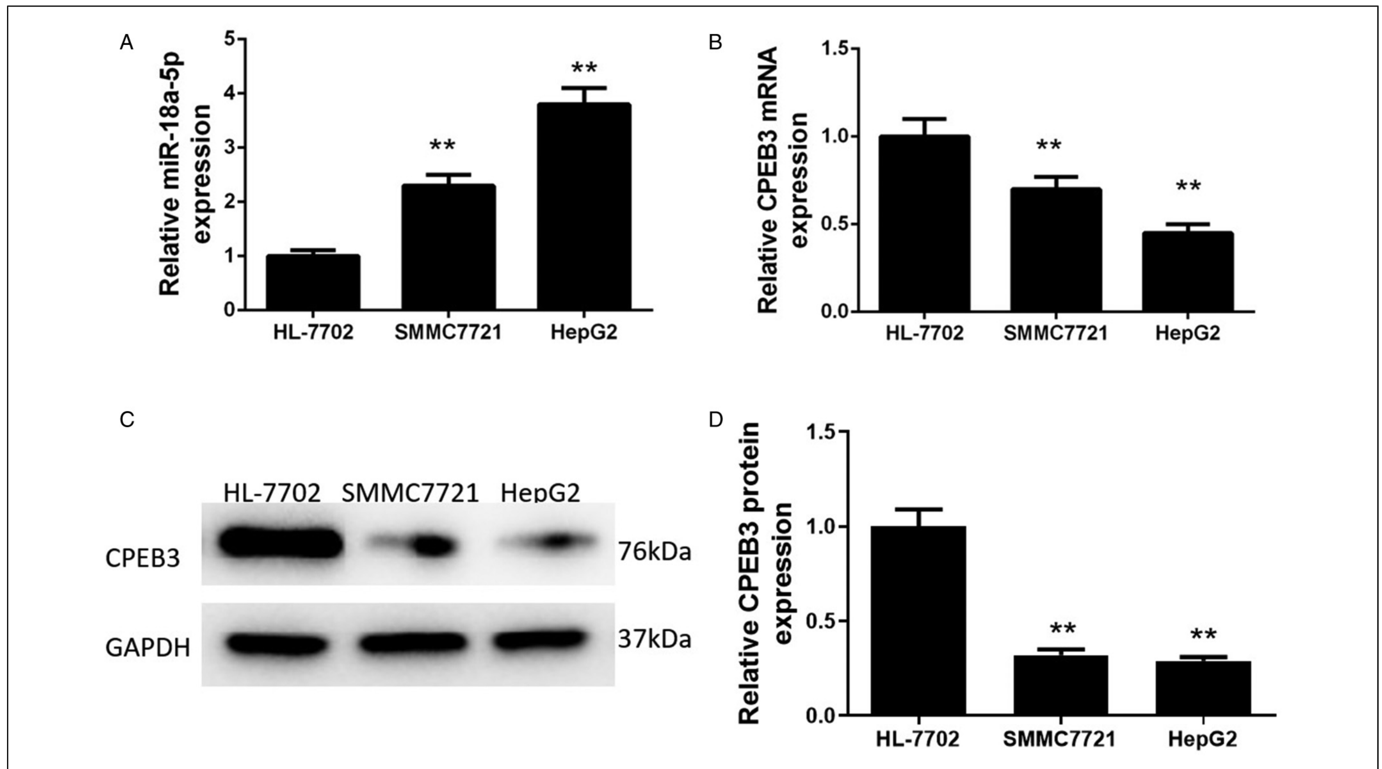

Figure 2. Expression of miR-18a-5p and CPEB3 in HCC cells. (A, B) MiR-18a-5p and CPEB3 mRNA expression in HL-7702, SMMC7721, and HepG2 cells; (C, D) CPEB3 protein expression in SMMC7721, HepG2 and HL-7702 cells; ** $P<.01$.

mean ± standard deviation. Two groups were compared by Student's *t*-test. One-way analysis of variance (ANOVA) was used to compare differences among the groups. $P<.05$ indicated statistically significant.

Results

MiR-18a-5p Negatively Correlates CPEB3 in HCC

A total of 126 differential miRNAs were obtained (Figure 1A), and miR-18a-5p was remarkably up-regulated in HCC tissue (Figure 1B). MiR-18a-5p expression was inversely correlated with the prognosis of HCC indicated by survival analysis (Figure 1C). It was reported that miR-18a can promote the progression of a variety of cancers, and serves as a prognostic factor.[19-22] However, there are few relevant studies on the regulation of miR-18a-5p in the malignant development of HCC cells. Hence, miR-18a-5p was chosen as the study object. A total of 1981 differential mRNAs were obtained (Figure 1D). Potential targets of miR-18a-5p were analyzed by databases, and 4 candidates (CPEB3, CYP39A1, ESR1, and GPM6A) were obtained finally from the intersection (Figure 1E). Pearson correlation analysis result manifested that miR-18a-5p was significantly inversely correlated with CPEB3 and ESR1 expression (Figure 1F and G). The role of miR-18a-5p and ESR1 in liver cancer has been clearly reported.[19] Hence, CPEB3 was chosen for further analysis. As analyzed, CPEB3 expression was significantly low in HCC tissue, and the overall survival of those patients was poor (Figure 1G and H). The above results suggested that miR-18a-5p is likely to regulate the occurrence of HCC by targeting CPEB3.

MiR-18a-5p Expression is High While CPEB3 Expression is Low in HCC Cells

The qRT-PCR result showed that miR-18a-5p in SMMC7721 and HepG2 cells was notably up-regulated (Figure 2A). While CPEB3 mRNA and protein levels in HCC cells were significantly down-regulated (Figure 2B to D).

MiR-18a-5p Modulates Progression of HCC Cells

We overexpressed and silenced miR-18a-5p in SMMC7721 and HepG2 cells to observe the role of miR-18a-5p in the malignant progression of HCC cells. The qRT-PCR result showed that miR-18a-5p in the mimic group was significantly up-regulated, while that in the inhibitor group was decreased (Figure 3A to G). The proliferation, migration, and invasion of cells were noted to be significantly up-regulated in SMMC7721 and HepG2 cell lines overexpressing miR-18a-5p compared with those of the control group (Figure 3B to F). Down-regulation of miR-18a-5p expression significantly suppressed the progression of HCC cells (Figure 3H to L).

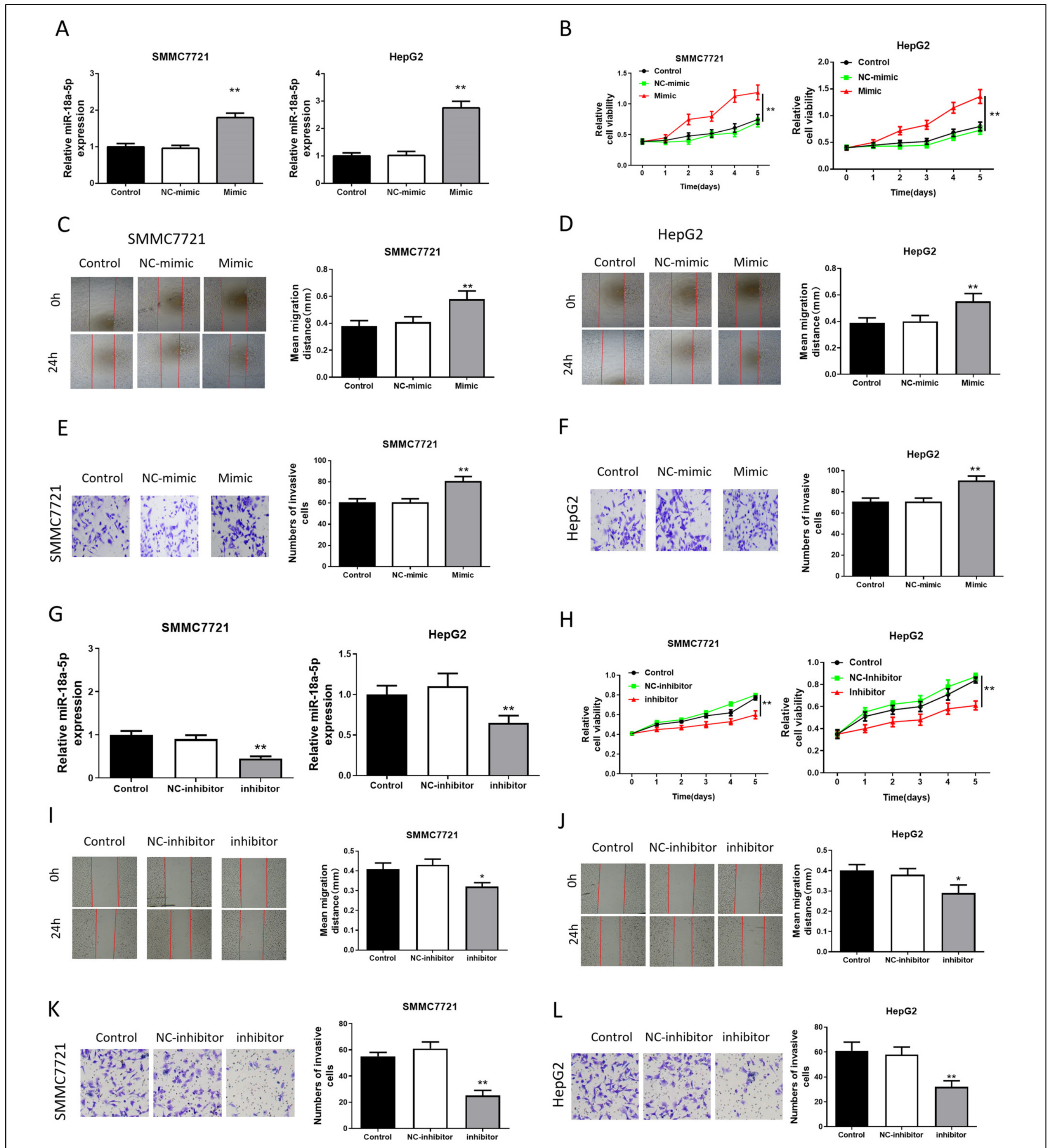

Figure 3. MiR-18a-5p accelerates HCC cell growth. (A, G) MiR-18a-5p expression in each treatment group detected by qRT-PCR; (B) Proliferative capacity of SMMC7721 and HepG2 overexpressing miR-18a-5p detected by MTT assay; (C, D) Migratory capacity of SMMC7721 and HepG2 cells with overexpression of miR-18a-5p detected using wound healing assay; (E, F) Transwell assay detected the invasive capacity of SMMC7721 and HepG2 cells under overexpression of miR-18a-5p; (H) MTT assay was used to detect the proliferation of SMMC7721 and HepG2 cells after the down-regulation of miR-18a-5p expression; (I, J) Migration ability of SMMC7721 and HepG2 cells after down-regulation of miR-18a-5p expression was detected by wound healing assay; (K, L) Transwell assay was used to detect the invasive ability of SMMC7721 and HepG2 cells after down-regulating miR-18a-5p; ** $P < .01$.

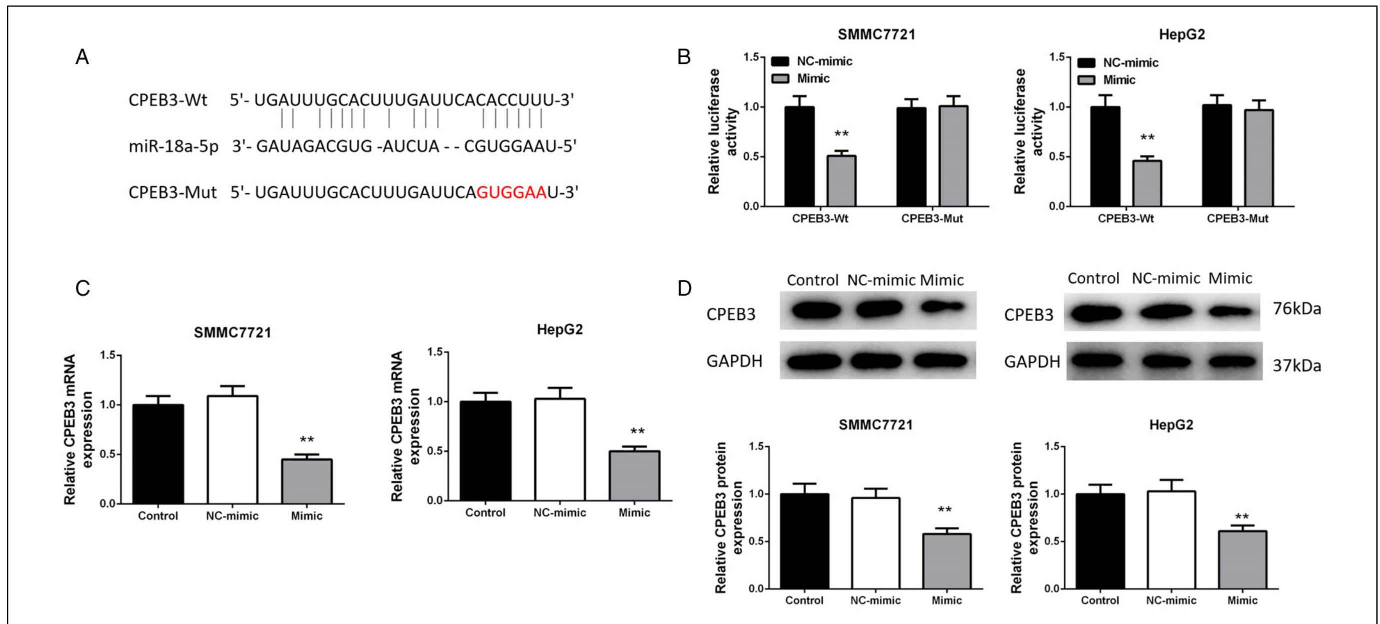

Figure 4. MiR-18a-5p targets and suppresses CPEB3**.** (A) Putative target binding sites of miR-18a-5p and CPEB3; (B) Luciferase activity in different treatment groups with overexpressed miR-18a-5p; (C) Expression of CPEB3 mRNA in SMMC7721 and HepG2 cells upon miR-18a-5p overexpression; (D) Protein expression of CPEB3 in SMMC7721 and HepG2 cells under miR-18a-5p overexpression; ** $P < .01$.

In HCC, miR-18a-5p Targets CPEB3 Expression

Putative binding sites of miR-18a-5p on CPEB3 3′UTR were observed by starBase database (Figure 4A). The results of the dual-luciferase assay also supported the above prediction results. Overexpression of miR-18a-5p significantly inhibited luciferase activity in the wild group, but hardly affected the activity of the mutant group (Figure 4B). Subsequently, CPEB3 expression in SMMC7721 and HepG2 cells overexpressing miR-18a-5p was significantly down-regulated (Figure 4C and D).

MiR-18a-5p Promotes Progression of HCC Cells by Targeting CPEB3

Next, we overexpressed miR-18a-5p and CPEB3 in SMMC7721 and HepG2 cell lines to analyze whether miR-18a-5p promotes the development of HCC cells by inhibiting CPEB3. The mRNA and protein levels of CPEB3 were greatly down-regulated under overexpression of miR-18a-5p, while no significant difference was there between the control group and the mimic + CPEB3 group (Figure 5A and B). We further discovered that the cell proliferative, migratory, and invasive abilities were all significantly up-regulated upon the overexpression of miR-18a-5p. Nevertheless, when miR-18a-5p and CPEB3 were overexpressed at the same time, the above-enhanced abilities of SMMC7721 and HepG2 cell lines recovered to a level similar to the control group with no difference (Figure 5C to F).

Discussion

HCC has approximately 745 000 deaths each year.[23] The overall survival rate within 5 years for HCC patients is about 30%.[14,23] Therefore, improving the survival of HCC sufferers remains to be a major challenge. It is reported that miRNAs often present dysregulated expression in tumors.[24] This also suggests that miRNA may become a potential target for the development of chemotherapeutic drugs in the future. Abnormal expression of miRNAs was discussed in HCC.[23,25–27] Studies showed that miR-18a regulates the occurrence of various cancers, including colorectal cancer,[6] gastric cancer,[9] lung cancer,[8] and HCC.[7] Although it is proposed that miR-18a promotes proliferation and metastasis of HCC by inhibiting target genes,[14,28] its mechanism in HCC has not been completely studied. Here, we first analyzed miR-18a-5p expression in HCC and explored its role in cell biological functions. MiR-18a-5p was up-regulated in HCC, and its overexpression significantly promoted cell growth. The above results are in accordance with previous studies, which further prove that miR-18a-5p is an oncogene in HCC.

Present literature has confirmed that CPEB3 is vital in the progression of HCC.[29] For example, the study of Zhang et al[18] showed that CPEB3 can restrain EMT of HCC cells, and mice with CPEB3 knockout were more prone to develop liver cancer and lung metastasis. MiR-224 performs a tumor-promoting effect in HCC malignancies by targeting CPEB3.[16] In addition, some studies have shown that CPEB3 is associated with signaling pathways that are critical for cancer proliferation and metastasis. Fang et al[30] discovered that the anti-tumor effect of CPEB3 in colorectal cancer may be mediated by the regulation of the JAK/STAT pathway. Zhong et al[31] found in their study that CPEB3 can inhibit EMT by inhibiting IL-6/IL-6R/STAT3 in colorectal cancer cells. These suggest that CPEB3 inhibits the development of cancer by regulating a variety of signal transduction. However, the correlation between

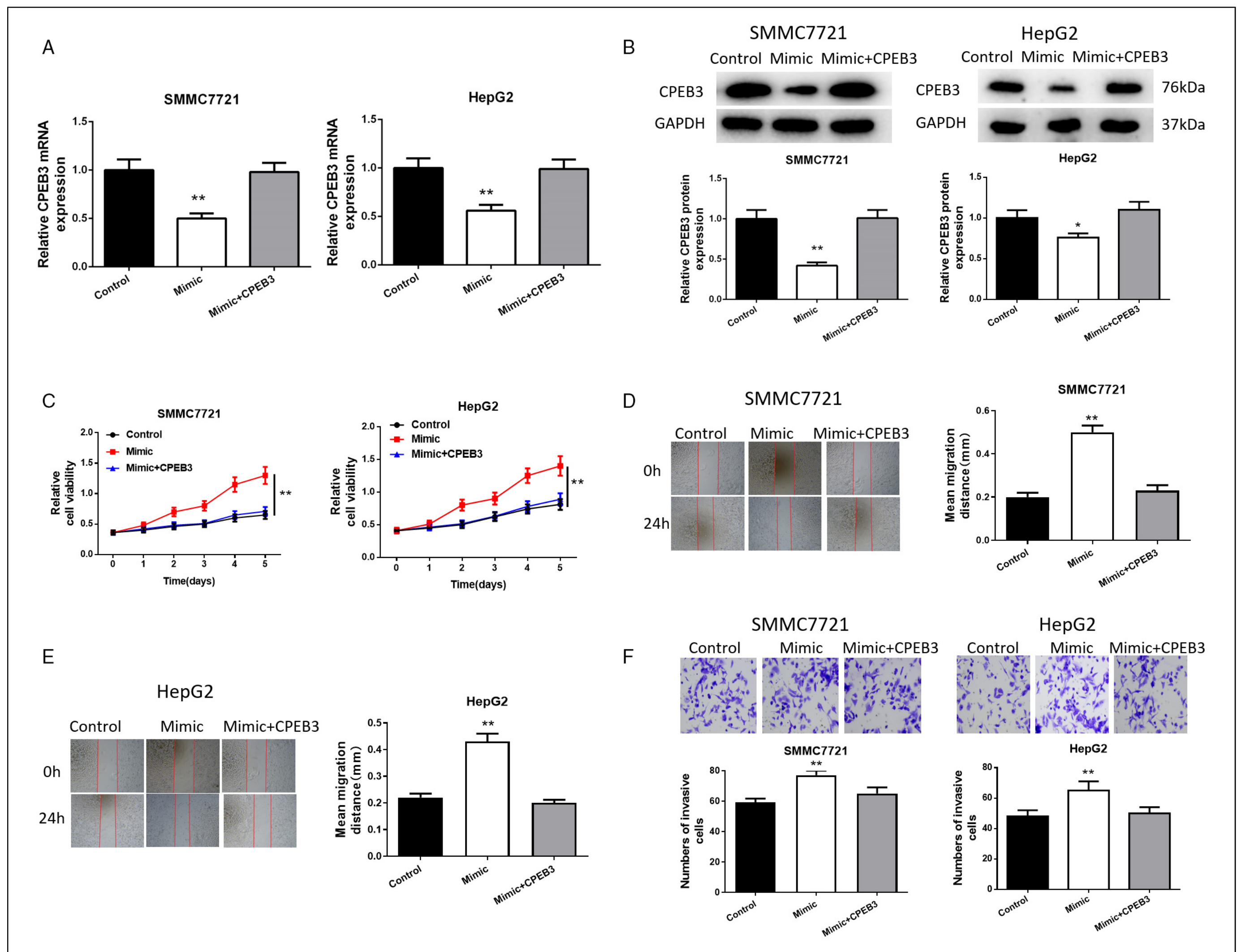

Figure 5. MiR-18a-5p suppresses CPEB3 expression and promotes the progression of HCC cells. (A) Expression of CPEB3 mRNA in Control, Mimic and Mimic + CPEB3 groups; (B) CPEB3 protein expression in different treatment groups; (C) The proliferative capacity of SMMC7721 and HepG2 cells; (D-E) The migratory ability of SMMC7721 and HepG2 cells; (F) The invasive ability of SMMC7721 and HepG2 cells; *$P < .05$ and ** $P < .01$.

miR-18a-5p and CPEB3 in HCC has not been reported. We found in this study that CPEB3 in HCC was significantly down-regulated. This is consistent with the findings of Shu et al[29] Besides, we validated at the molecular level and cellular level, and found that miR-18a-5p could reduce CPEB3 expression. MiR-18a-5p promoted the progression of HCC cells through negatively regulating CPEB3. Therefore, this in vitro experiment further supports the idea that miR-18a-5p facilitates the occurrence of liver cancer.

In conclusion, this study proved that miR-18a-5p enhanced the progression of HCC cells by down-regulating CPEB3. The result helps people better understand the mechanism of miR-18a-5p underlying HCC progression, and also helps to find an entry point for searching into new targeted therapeutic approaches for HCC. However, due to the few studies on miR-18a-5p and CPEB3 in liver cancer progression, many issues remain unanswered. For instance, the specific signal transduction pathway mediated by miR-18a-5p in promoting HCC progression via targeting CPEB3 is still undefined. Therefore, further exploring the specific downstream regulatory mechanisms in HCC is necessary.

Authors' Note

Dr MX C and Dr FZ Q contributed to the study design. Dr LB W and Dr XG L acquired the data and performed data analysis. Dr MX C and Dr DM C wrote the article. Dr FZ Q, Dr MX C and Dr XG L revised the article. Dr XG L gave the final approval of the version to be submitted. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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